COMPARATIVE STUDY OF THE EFFICACY OF 3 WEEKS vs 2 WEEKS AMPHOTERICIN THERAPY IN HIV POSITIVE CRYPTOCOCCAL MENINGITIS PATIENTS & ALSO ASCERTAIN THE IMPACT OF BOTH ON CSF PARAMETERS

Dissertation Submitted to
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CERTIFICATE

This is to certify that this dissertation entitled "**COMPARATIVE STUDY OF THE EFFICACY OF 3 WEEKS AMPHOTERICIN THERAPY vs 2 WEEKS AMPHOTERICIN THERAPY IN HIV POSITIVE CRYPTOCOCCAL MENINGITIS PATIENTS "** submitted by **Dr.R.ISRAEL,** to the Tamil Nadu Dr. M.G.R. Medical University Chennai is in partial fulfillment of the regulations for the award of M.D. DEGREE BRANCH –I (General Medicine) and is a bonafide research work carried out by him under direct supervision and guidance.

Signature of the Unit Chief &Guide

Signature of Professor & HOD

Signature of Dean

DECLARATION

I solemnly declare that the dissertation titled **"COMPARATIVE STUDY OF THE EFFICACY OF 3 WEEKS AMPHOTERICIN THERAPY vs 2 WEEKS AMPHOTERICIN THERAPY IN HIV POSITIVE CRYPTOCOCCAL MENINGITIS PATIENTS"** was done by me at Stanley Medical College and Hospital during 2008-2010 under guidance and supervision of **Prof.Dr. S.MAGESH KUMAR**. **M.D.,**

The dissertation of submitted to the Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfillment of requirement for the award of M.D. DEGREE (BRANCH-I) in General Medicine.

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CONTENTS

INTRODUCTION

The HIV pandemic has raised the profile of *Cryptococcus neoformans* from obscure yeast to the most important fungal cause of morbidity and death worldwide. Previously described as a rare cause of meningitis in the tropics, or in patients with some form of acquired immunodeficiency such as haematological malignancy or organ transplantation, cryptococcal meningitis is now a significant public health burden in developing countries.

20% of all AIDS deaths are due to cryptococcal meningitis, making it the second most common cause of death in HIV infection after tuberculosis[1]. Moreover, despite the availability of highly active antiretroviral therapy (HAART), it continues to pose difficult management questions in the industrialized world.

Mortality from developed countries, secondary to HIV associated cryptococcal meningitis is in the range if 10-30% while in the developing countries the mortality is substantial, around 30-40% because of late presentation, limited access to antifungal therapy and inability to adequately monitoring intracranial pressure among many reasons[2].

Treatment with flucytosine plus Amphotericin B is recommended in many reference books and guidelines[3, 4]. The addition of flucytosine results in faster sterilization of the CSF and fewer relapses than with the use of

Amphotericin B alone. Since, flucytosine is not availability in developing countries. We forced to use the Amphotricin B as initial drug of choice.

Recommended 2-week induction treatment with Amphotericin B monotherapy for HIV patients with cryptococcal meningitis in resource-limited settings may be suboptimal. Extending the therapy to 3 weeks is likely to result in sterilization of the CSF in a majority of patients[5].

Questions remain for physicians regarding the optimal combination of antifungal agents, duration of treatment, accurate indicators of response to therapy.

Hence, this study is an attempt to throw light on treatment scenario of cryptococcal meningitis in HIV sero-positive patients.

REVIEW OF LITERATURE

Cryptococcal meningitis has emerged as a leading cause of infectious morbidity and mortality in patients with AIDS. It is the second most common cause of opportunistic neuro-infection among HIV sero-positive patients.

CRYPTOCOCCUS

The genus *Cryptococcus* contains at least 39 species of yeast, but few are able to cause disease in humans[6] (Casadevall & Perfect 1998). Even those that do cause infection are not primarily pathogens, they have so-called 'ready-made virulence' as a side-effect of their adaptation to their environments.

Most human infections are due to *C. neoformans*. Disease has very rarely been attributed to other species such as *C. flavescens* (formerly *laurentii*).

C. neoformans is an encapsulated yeast first identified as a human pathogen in 1894 when it was isolated from the tibia of a patient in Germany by Busse and Buschke[7] (Mitchell & Perfect 1995). The same year it was also isolated from peach juice by Sanfelice[8] (Mitchell & Perfect 1995).

The first description of cryptococcal meningitis was published in 1905 by von Hansemann, although a case of chronic meningitis described in 1861 by

Zenker, prior to the pathogen isolation, was probably the first case history[9, 10] (Mitchell & Perfect 1995; Casadevall & Perfect 1998).

MICROBIOLOGY

Cryptococcus neoformans is dimorphic, existing in the asexual yeast form characterized by oval to spherical cells with a polysaccharide capsule, and in the sexual or perfect state characterized by the presence of basidiospores. The sexual form has not been described in association with clinical specimens and is observed only during mating and mating has only been observed under laboratory conditions. The asexual form reproduces through budding, which is frequently seen in clinical specimens. Some strains produce pseudohyphal forms that may be seen in tissue sections.

C. neoformans is readily cultured in the laboratory, producing mucoid colonies within 36–72 h, although growth is inhibited at 37 °C. Colonies are white to cream in colour, but characteristic dark brown colonies are formed when grown on birdseed agar. The organism grows readily in automated blood culture systems.

There are three varietal forms of *C. neoformans – C. neoformans var grubii*, *C. neoformans var gattii*, and *C. neoformans var neoformans*. They are distinguishable by serotyping using rabbit antisera, and by DNA fingerprinting techniques such as amplified fragment length polymorphism analysis[11, 12]

(Boekhout *et al*. 1997; Boekhout *et al*. 2001). The different varietal forms are now thought to represent different species[13] (Franzot *et al*. 1999). They have different environmental niches, geographical distributions, and affect different patient groups (Table 1).

Table 1. varietal forms of Cryptococcal neoformans

PATHOGEN	SEROTYPE	GEOGRAPHIC DISTRIBUTION	ENVIRONMENTAL ASSOCIATION	AFFECTED PATIENT GROUPS
C. neoformans var grubii	A	Worldwide	Birds, particularly pigeon excreta	HIV patients (98% of all isolates), Immuno-suppressed patients Rarely immune-competent
C. neoformans var gattii	B,C	Tropic and subtropics	Flowering eucalyptus trees	Immuno-competent patients
C. neoformans var neoformans	D	World wide	Birds, particularly pigeon excreta	Immune suppressant and rarely immune-competent
C. neoformans var grubii/var neoformans hybrid	A,D	Not known	Not known	Rare clinical isolates immuno-suppressed

The vast majority of infections world-wide occur in HIV patients and are due to serotype A (*C. neoformans var grubii*). In the absence of serotyping, *var gattii* can be distinguished from *var neoformans* and *var grubii* through growth on canavanine glycine-bromothymol blue agar.

C. neoformans var grubii* and *C.neoformans var neoformans Both these varieties predominantly affect the immunosuppressed, and *var grubii* (serotype A) is responsible for the vast majority of infections in HIV-positive patients. Their ecological niche is not well defined, but *C. neoformans* is not primarily a pathogen. It is associated with pigeon droppings and soil. Birds are not thought to develop disease because of their relatively high body temperature, which inhibits the growth of *Cryptococcus*.

C. neoformans var gattii This variety occurs in the tropics and subtropics and is found in association with flowering eucalyptus trees such as the red river gum (*Eucalyptus camaldulensis*) (Ellis & Pfeiffer 1990). Disease predominantly occurs in immunocompetent patients and there is a strong male preponderance (Chen *et al*. 2000). Interestingly, there has recently been an outbreak of this infection on Vancouver Island, British Columbia, where the climate is far from subtropical.

Mammals other than humans are susceptible to infection with this organism and, perhaps unsurprisingly, infection in koala bears is well documented. However, disease has also been recorded in dolphins in the Vancouver Island outbreak.

SPECTRUM OF DISEASE

While meningitis is by far the most common manifestation of cryptococcal infection, other infectious syndromes are well recognized. They will be described briefly below, but the focus of this study will be on meningitis. Infection is believed to occur through inhalation and the primary site of infection is the lung. It is likely that most such infection is asymptomatic. Primary infection may result in either immediate pulmonary or disseminated disease, or it may be quiescent for many years, with subsequent disease development following an immunosuppressive event later in life. Many of the early case reports were of patients with cancer. Disease has been described in almost all body systems – the first case report was of osteomyelitis, but the brain remains the organ with a particular vulnerability to infection for reasons that are not well understood.

CENTRAL NERVOUS SYSTEM

Meningitis is the most common manifestation of cryptococcal infection. It would be more accurate to describe the syndrome as a meningoencephalitis,

since histopathological examination demonstrates that along with the subarachnoid space the brain parenchyma itself is usually involved (Lee *et al*. 1996). Presentation varies, and the diagnosis should be considered in all cases of subacute meningitis (presentation over 2–4 weeks). However, the organism can also cause an acute meningitis occurring over a few days to a week, and a true chronic meningitis, the longest duration of illness recorded being 29 years(Casadevall & Perfect 1998). Other neurological presentations include focal signs secondary to cryptococcoma development, as well as subdural effusions and spinal cord lesions secondary to granuloma. It is important to remember that as well as causing meningitis, cryptococcal infection is one of the causes of reversible subacute dementia (perhaps because of the hydrocephalus although yeasts are found in brain parenchyma), and the diagnosis should be excluded in those patients with a relevant exposure history, such as travel to the tropics, or risk of immunosuppression. Endophthalmitis can occur alone or as part of meningitis. Blindness is a common sequelae of infection, particularly in Viet Nam in apparently immunocompetent patients.

Lung

The lung is the second most common organ to develop clinical disease usually pneumonia, which can occur in the immunocompetent, particularly with *var gattii* infection. Other pulmonary manifestations include solitary nodules, superior vena cava obstruction, cavitation and pleural effusions/empyema – the

radiographic appearances can be very similar to pulmonary tuberculosis. HIV patients who are infected with *C. neoformans* tend to present with meningitis rather than pulmonary disease. Although up to one-third of them have an abnormal chest Xray, pulmonary symptoms are rare (Casadevall & Perfect 1998). *Var gattii* much more commonly causes pulmonary disease (without meningitis) in immunocompetent patients, resembling pulmonary TB. It is extremely unusual for HIV patients to get symptomatic pulmonary disease due to cryptococcal infection.

Skin

The skin is the third most common organ to be affected by cryptococcal infection. Infected skin lesions can have a wide variety of appearances,from papules through to plaques, subcutaneous swellings, sinuses and blisters.Skin involvement appears to be becoming more common with HIV infection and the lesions often resemble molluscum contagiosum. In fact, other skin diseases may coexist within the same lesion (for example Kaposi's sarcoma). While skin infection can occur following inoculation, for example through needle stick injury, it is generally the result of disseminated cryptococcal infection and so other sites of potential infection such as brain, heart and lungs should be investigated.

EPIDEMIOLOGY OF CRYPTOCOCCAL MENINGITIS

Cryptococcosis is a rare infection in healthy human populations. Therefore the prevalence of cryptococcal disease in a population can be considered as an indicator of the degree of immune suppression in that group. Indeed, cryptococcal meningitis is a sentinel for the spread of the HIV pandemic. In common with many hospitals in Asian countries, the Hospital for Tropical Diseases in Ho Chi Minh City has seen a large rise in the number of clinical isolates of *C.neoformans* over recent years that represents the spread of HIV within our community.

The HIV pandemic has lead to a massive increase in the number of cases of cryptococcal meningitis. Generally, there appears to be a preponderance of males affected, even after adjusting for sex differences in HIV infection, and most cases occur in the 20–50 years old age group (Lewis & Rabinovich 1972). Cryptococcosis is rare in children. Conditions other than HIV that predisposeto infection include:

• immunosuppressive therapy associated with organ transplantation;

• sarcoidosis;

• lymphoproliferative disorder;

• hypogammaglobulinaemia;

• corticosteroid therapy;

• systemic lupus erythematosus;

• cirrhosis;

• peritoneal dialysis (Casadevall & Perfect 1998).

The effect of diabetes mellitus on predisposition to cryptococcal meningitis is unclear. Apparently normal patients who develop invasive cryptococcal disease due to serotypes A or D may have some underlying unidentified subtle immune defect (Schimpff & Bennett 1975). However, invasive cryptococcosis due to serotypes A or D probably does occur in otherwise normal individuals, and the incidence is estimated at 0.2 per million people per year (Friedman 1983).

THE HIV PANDEMIC

The HIV pandemic has such a profound impact on the prevalence of cryptococcal disease that it is important to understand its scale. Currently there are 40 million people living with HIV/ AIDS (UNAIDS/WHO 2003). The vast majority (27 million) of these are in sub-Saharan Africa where the overall seroprevalence is 7.5–8.5% of 15–49 years old but this rises to 45% in some countries. There are 6 million people living with HIV in south and south-east

Asia. In 2003 there were 3 million HIV deaths and 5 million new infections worldwide. The epidemic continues to grow rapidly, particularly in south and south-east Asia (up to 1.1 million new infections in 2003) and Russia. Recently it was estimated that in Botswana, where HIV seroprevalence approaches 45%, 9 out of 10 of the current 15- year-old boys will die from HIV infection. In Ho Chi Minh City, Viet Nam, more than 80% of intravenous drug users were HIV positive by the end of 2001.

HIV infection leads to a progressive inexorable fall in CD4 count. A CD4 count of less than 100 cells/μL (normal range 500–1500 cells/μL) dramatically increases the risk of cryptococcal meningitis. In much of the developing world lack of access to HIV testing and health education means that many patients have CD4 counts substantially lower than this when they present to health services, and so they are already severely immunosuppressed. It should be remembered that absolute CD4 counts should only be taken as a guide to help generate differential diagnoses – individual patients can lose disease-specific immune responses yet have relatively well-preserved CD4 counts, and therefore be at risk of opportunistic infections. While Highly Active Anti-Retroviral Therapy (HAART) is effective in producing meaningful immune reconstitution, it is unavailable to the vast majority of people infected with HIV due to cost and lack of political will. Thus there will be a large rise in the incidence of tuberculosis and opportunistic infections as the pandemic progresses. For

example, in parts of Africa up to 90% of adult in-patients on general medical wards are HIV positive, and in Zimbabwe 45% of all meningitis is caused by *Cryptococcus neoformans* (Mwaba *et al*. 2001).

CLINICAL PRESENTATION OF CRYPTOCOCCAL MENINGITS

The presentation varies. The most frequent symptom in both the immunosuppressed and immunocompetent is headache, occurring in more than 75% of patients. Fever is also common, occurring in more than half of all cases.

The duration of symptoms before presentation is likely to be longer in non-AIDS patients, with a history of more than 2 weeks in only 25% of HIV positive patients. Other common symptoms include nausea and vomiting, lethargy, personality change, memory loss, stupor and coma (Casadevall & Perfect 1998). Neck rigidity seems to be uncommon in HIV patients, occurring in approximately 25%, and focal neurological signs appear in 20% (Friedmann *et al*. 1995).

Some African series have reported a higher prevalence of neck stiffness (Moosa & Coovadia 1997). Skin lesions are reported in between 3 and 10% of HIV infected patients. In general, focal neurological signs, neurological sequelae and lung involvement are more common in *vargattii* infections than in *var grubii* or *var neoformans* infections (Casadevall & Perfect 1998).

CSF EXAMINATION

Definitive diagnosis of cryptococcal meningitis requires lumbar puncture with demonstration of yeasts with India ink stain, positive cryptococcal antigen testing or culture of the organism. CSF examination generally reveals a mild mononuclear leucocytosis (50–500 cells/μL). The CSF protein is rarely greater than 500–1000 mg/Dl and it may be normal, especially in HIV patients.

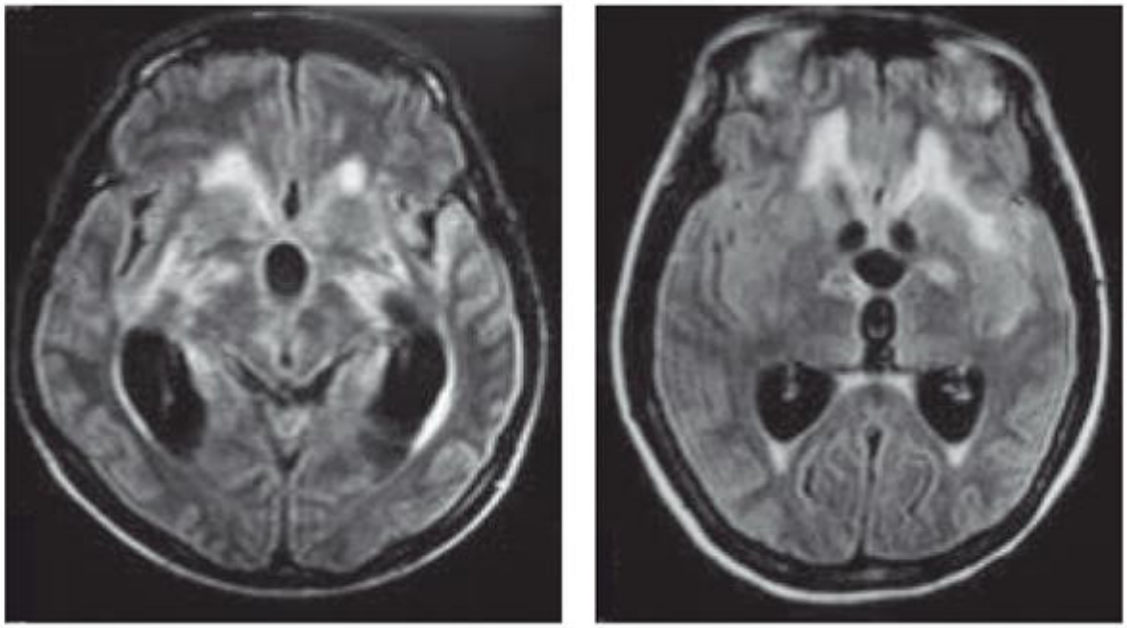
In HIV patients, the cell count is usually much lower, and often in single figures. CSF glucose/ blood glucose is usually slightly low. One study from Africa found that 17% of AIDS patients with cryptococcal meningitis had normal CSF parameters (Moosa & Coovadia 1997). Clues to HIV infection on routine blood testing include mild anaemia, lymphopenia, thrombocytopenia and raised total protein.

IMAGING

CT brain scan is normal in 50% of patients with cryptococcal meningitis. There are no pathognomonic findings, and the changes may closely resemble those seen in tuberculous meningitis.

The most common abnormal finding is hydrocephalus. Magnetic resonance imaging is more likely to demonstrate abnormalities than CT scanning. The appearances may differ depending on the cause of any underlying immunosuppression. For example, in AIDS patients there may be diffuse

cortical atrophy, and hydrocephalus is reportedly less common. Cortical atrophy in HIV patients may be a direct consequence of the retroviral infection. Conversely, gyral enhancement is often seen in HIV negative patients. Occasionally focal abnormalities representing cryptococcomas will be seen. Brain imaging is justified to exclude mass lesions and, in the HIV population, other pathology such as toxoplasmosis or CNS lymphoma. The role of serial scans in monitoring response to treatment is unclear (Casadevall & Perfect 1998).



MRI scan of the brain with cryptococcal meningitis (a) compared with MRI scan of a patient with tuberculous meningitis (b) showing prominent dilated ventricles with periventricular high signal.

DIAGNOSTIC TECHNIQUES

India ink test

The CSF India ink test is a simple and relatively sensitive test that enables the rapid diagnosis of cryptococcal meningitis. Its low cost makes it suitable for resource-poor settings. A drop of CSF is placed on a slide and mixed with a drop of India ink. A cover slip is placed on the slide, which is examined under an oil immersion lens. Yeast cells are easily identified through the halo effect that occurs around them because of the glucuronoxylomannan capsule (Fig. 4). The sensitivity of the test rises to 75% with centrifugation of the clinical sample. However, a concentration of yeasts less than 104 colony forming units (CFU) is unlikely to be detected, and therefore all patients should have CSF fungal culture and cryptococcal antigen testing if resources allow. It is important to note varied that tuberculous meningitis may occur at the same time as cryptococcal meningitis in AIDS patients, and therefore all patients should have a CSF smear examined for acid and alcohol fast bacilli to exclude TB.

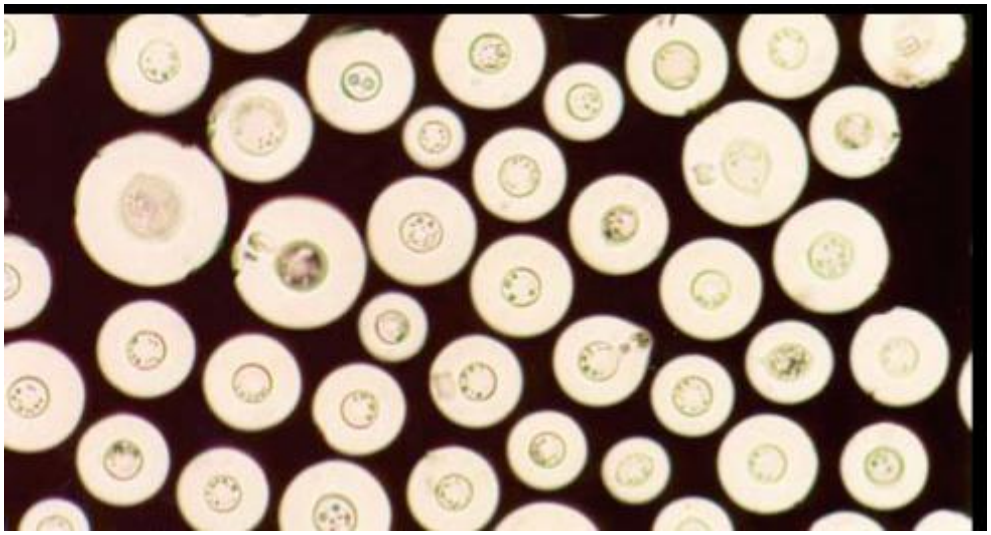


Fig-1 India ink stain of CSF demonstrating many yeast cells of C.Neoformans with prominent capsule.

Culture

C. neoformans from CSF or blood grows readily on blood or Sabouraud's agar at 35 °C. Identification can be confirmed through the demonstration of capsule growth on corn meal agar, development of characteristic brown mucoid colonies on birdseed agar, and through commercially available sugar assimilation test kits.

Biotyping, to distinguish *var gattii* from *var neoformans* and *var grubii*, can be done relatively cheaply using canavanine-glycine-bromothymol blue agar, although currently this has little clinical relevance. *C. neoformans* grows easily in commercially available automated blood culture systems. Culture of CSF is more sensitive in detecting cryptococcal infection than the India ink test,

with a sensitivity approaching 90%. Positive culture is more likely with larger volumes of CSF.

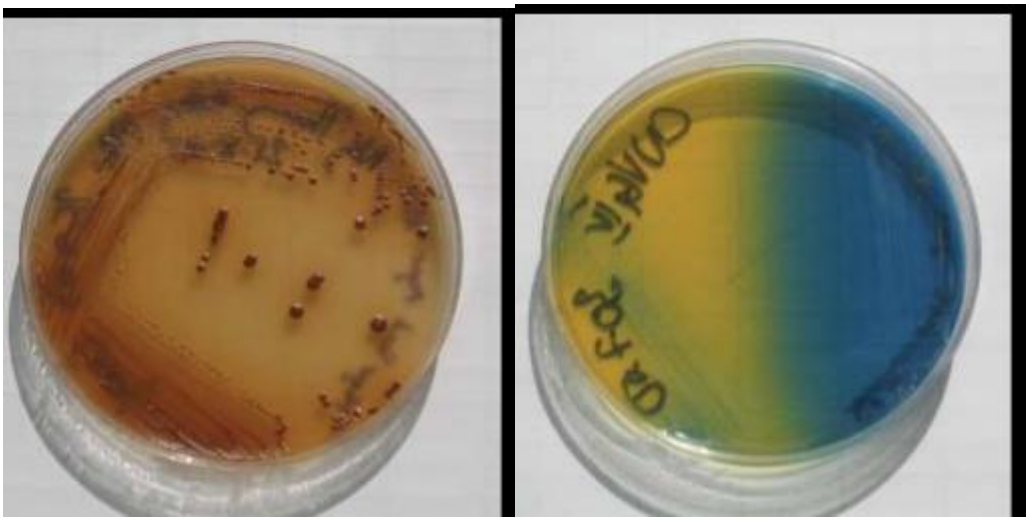


Figure 2 (a) Brown mucoid colonies of *C. neoformans* on birdseed agar and (b) blue discoloration of CGB agar by *C. neoformans var gattii*

Cryptococcal antigen

Cryptococcal antigen testing is both sensitive and specifi c in identifying patients with cryptococcal disease. Several commercial kits are available, relying on either latex agglutination

or ELISA methodologies. The kits can be used on serum or CSF and the sensitivity in CSF is greater than 90% in cryptococcal meningitis.

Their sensitivity with blood testing has probably been overstated. The kits have been designed primarily as qualitative diagnostic tests rather than as tools to quantify the amount of antigen present. However, they can be adapted to

offer semiquantitative information and there has been interest in using the tests to assess individual patient response to treatment. However it is difficult to ensure consistency between different patient samples, or over time with the same patient, and quantitative cryptococcal antigen measurement has so far proved disappointing as a clinical tool to measure response to treatment (Aberg *et al*. 2000).

Serotyping

There are immunotyping kits to distinguish the various cryptococcal serotypes. However, they are expensive, and currently patient management is more likely to be altered through knowledge of their underlying immune status.

Distinction between *vargattii* and other varieties can be satisfactorily determined using biotyping agar.

TREATMENT

Anti-fungal drug options for cryptococcal disease are limited. **Amphotericin B** is the mainstay of treatment.

This broad spectrum drug is fungicidal and *in vitro* resistance is extremely rare. However, nephrotoxicity is a significant problem, although is usually reversible if the total dose does not exceed 4 g (Khoo *et al*. 1994). It is exacerbated by salt depletion, and it has been suggested that patients should receive a normal saline infusion prior to amphotericin administration. Bioavailablity is extremely poor via the oral route and it must be given intravenously. It has curious and poorly understood pharmacokinetics – despite being undetectable in CSF it is effective in cryptococcal meningitis. Amphotericin B causes membrane disruption through binding to sterols in the cell membrane, but it probably also has an effect through stimulating macrophage function. It can be given intrathecally, but this is recommended only as part of salvage therapy for relapsed patients. The lipid formulations of amphotericin B have the advantage of lower toxicities, and can be given in higher dosage of up to 10 mg/kg/day. However, they are considerably more expensive.

Flucytosine is a nucleotide analogue. Available in oral and intravenous formulations, it appears to have a synergistic action with amphotericin *in vitro*

(Schwarz *et al*. 2003). A randomised trial showed a trend towards more rapid CSF sterilization in patients receiving flucytosine in combination with amphotericin compared with amphotericin alone (van derHorst *et al.* 1997). Flucytosine is converted to fluoro-uracil within the fungal cell, and this is the active drug. It has the disadvantages of high cost, poor tolerability, rapid development of resistance if used as monotherapy, and the need to monitor blood levels.

The azole drugs (e.g.fluconazole) have revolutionized the treatment of fungal infections because of their potency, tolerability, good CSF penetration, and oral and intravenous formulations.Their mechanism of action is inhibition of sterol synthesis by the fungal cell so they may in theory adversely affect the action of amphotericin if used in combination. This has not been born out in animal studies, and there is now good data emerging from the treatment of systemic candidaemia that this is unlikely to be a problem (Rex *et al.* 2003). There is most experience with fluconazole in the treatment of cryptococcal meningitis. While it is not as potent as itraconazole *in vitro*, it has better CSF penetration and appears more effective in clinical trials (Saag *et al* 1999). The newer azoles such as voriconazole and posaconazole appear to have better *in vitro* activity against *C. neoformans* than fluconazole, but there are no data from controlled trials in cryptococcal meningitis.

Unfortunately the newer classes of antifungal agents such as caspofungin do not appear to have good activity against *C. neoformans.*

CURRENT TREATMENT GUIDELINES

Treatment guidelines were published for cryptococcal meningitis in 2000 (Saag *et al*. 2000). There are three phases – induction, consolidation and maintenance (also known as secondary prophylaxis). The guidelines A are largely based upon conclusions drawn from a double blind multicentre trial published in 1997 (van der Horst *et al*. 1997). This trial compared amphotericin alone vs. amphotericin combined with flucytosine for the initial 2 weeks of treatment, followed by either fluconazole or itraconazole for 8 weeks. It was not analysed on an intention-to-treat basis and a large number of patients appear to have been lost to follow up. The trial did not show any difference in clinical outcome between the treatment arms. Despite this, the study investigators recommended that amphotericin in combination with flucytosine be the first line treatment for cryptococcal meningitis. While there was a trend towards more rapid CSF sterilization in the combination treatment arm, and there is some *in vitro* evidence from other trials suggesting synergy between amphotericin and flucytosine,in fact the results from this trial were not robust enough to allow the investigators to make this recommendation. There is some evidence that in HIV negative patients the combination of flucytosine with amphotericin is beneficial, but these data relate to a much lower dose of amphotericin (0.3–0.4 mg/kg/day)

(Bennett *et al* 1979). There is no evidence that the combination of flucytosine with higher dose amphotericin is beneficial. Moreover, HIV positive patients are more likely to have adverse drug reactions with most of the antifungal drugs than HIV negative patients. There need to be more treatment trials in cryptococcal meningitis, but with the advent of HAART there is decreasing interest in this disease in industrialized countries.

Atul K Patel et al 2010 found that the recommended 2 weeks induction treatment with Amphotericin B monotherapy for HIV patients with cryptococcal meningitis in resource-limited settings may be suboptimal for at least one-third of the patients. Extending the therapy to 3 weeks is likely to result in sterilization of the CSF in a majority of these patients. This finding requires confirmation by a larger sample size in appropriately powered studies. Delaying ART initiation by at least 2 weeks after amphotericin B treatment may decrease the incidence of IRIS.

Once the first two phases of treatment have been completed, patients with HIV infection need to continue on long-term fluconazole maintenance therapy. The dose is 200 mg per day. The relapse rate with this regime is in the order of 2% per year. An alternative maintenance therapy is intermittent amphotericin, but this is less effective (Powderley 1992). There is increasing evidence that the rise in CD4 count observed with HAART provides meaningful anti-

cryptococcal immune reconstitution, and that it is probably safe to stop maintenance therapy once the CD4 count has risen above 100 cells/μL (Vibhagool *et al*. 2003). However, if the CD4 count falls below 100 cells/μL again, then most physicians would recommend the reintroduction of maintenance therapy.

There are less recent data regarding the optimal treatment of cryptococcal meningitis in non-HIV infected patients. In part this is due to the difficulty in gathering enough patients to perform adequately powered trials. It is not clear whether treatment should differ according to the infecting variety of *Cryptococcus*. Thus treatment recommendations tend to follow those for HIV positive patients. An alternative is to give amphotericin B 1 mg/kg/day for 6–10 weeks but this has the disadvantage of its inconvenient formulation and nephrotoxicity. If the patients are immunosuppressed they may need to continue maintenance treatment life-long. Wihout maintenance therapy there is a significant risk of disease relapse of 15–20%, and therefore close follow-up is mandatory.

Other than the clinical status of the patient and CSF sterilization, there are no satisfactory markers of response to treatment. The difficulties in the use of cryptococcal antigen titres have been described above. The interpretation of antigen levels in CSF is further complicated by the fact that the level is a function of the rate of production and removal. Antigen may be present in brain

parenchyma and leach into the CSF over some weeks. In HIV-negative patients, persistently high CSF cryptococcal antigen titres are predictive of relapse, but there are no precisely defined titre levels to help guide management decisions. In HIV-positive patients a rise in CSF cryptococcal antigen appears to predict relapse, but is otherwise of little use. Frequent clinical review and CSF examination is recommended.

COMPLICATIONS OF CRYPTOCOCCAL

MENINGITIS

Raised intracranial pressure

The commonest complication is raised intracranial pressure (ICP) which occurs in more than 50% of patients (Saag *et al*. 2000). This is probably due to impaired drainage of CSF by polysaccharide capsule. Among HIV-positive patients, a rise in ICP over the first 2 weeks of treatment is associated with a poor clinical response. Careful management of raised ICP is thought to reduce mortality. Current recommendations suggest that this is achieved through physical drainage of CSF, with repeated lumbar puncture, insertion of drains or ventriculo-peritoneal shunting but there have been no large-scale randomized trials of the impact of these interventions. It is not clear how frequently lumbar puncture should be performed for therapeutic drainage. The current recommendations are that lumbar puncture should be performed daily to keep

the CSF pressure within the normal range in those patients who have an ICP > 200 mm CSF until the pressure has been normal for several days. Mannitol has not been found to be useful in managing raised ICP. Published guidelines suggest that corticosteroids should be avoided in HIV-positive patients because of their high fungal burden and the potential for further immunosuppression. However, there are no data to confirm these recommendations.

There has also been interest in the use of acetazolamide as a treatment for raised ICP. The most recent controlled trial in HIV patients was stopped because of adverse events, including acidosis, in the active drug arm (Newton *et al* 2002). However, only a small number of patients had been recruited, and the trial needs to be repeated. It may be that the dose of acetazolamide at 1 g/day was too high.

Visual impairment

Blindness is common in cryptococcal meningitis, particularly in HIV-negative patients (Seaton *et al.* 1997b). It is thought to be due to raised intracranial pressure, direct invasion of the optic nerve, or adhesive arachnoiditis. There are some retrospective data that suggest that corticosteroids may be beneficial in HIV-negative patients with *var gattii* infections in reducing visual morbidity (Seaton *et al.* 1997a). The current treatment guidelines do not

recommend their use, but there have been recent trials in bacterial meningitis demonstrating their good safety profile, and a prospective trial is needed.

Cerebral infarction

Cerebral infarction is a recognized event in chronic meningitides such as tuberculous meningitis, and it is also recognized in cryptococcal meningitis (Lan *et al*. 2001). There is evidence from the murine model of cryptococcal meningitis that the anti-infammatory fibrinolytic agent pentoxifylline reduces mortality when used in combination with amphotericin B (Ostrosky- Zeichner *et al.* 1996). There are no data on the use of anti-infl ammatory drugs in humans with cryptococcosis.

IMMUNE RECONSTITUTION IN HIV

RELATED DISEASE

Over the past few years it has been recognized that patients with HIV can develop clinical syndromes, analogous to the paradoxical reactions seen during the treatment of tuberculosis, as they develop immune reconstitution as a result of starting HAART. A small number of cases of apparent immune reconstitution occurring in patients recently treated for cryptococcal meningitis have now been described (Jenny-Avital & Abadi 2002). The cases are usually sterile meningitides, and occurred up to 11 months after initiation of HAART. The clinical difficulty is indistinguishing relapsed disease from the reconstitution

syndrome. Consequently the patients were managed with antifungal treatment and continuation of HAART. As for most opportunistic infections, it is not yet clear whether it is better to begin antiretroviral therapy immediately, or to delay until the course of antifungal therapy is established or completed.

PROGNOSIS AND OUTCOME

Cryptococcal meningitis is universally fatal if untreated. With treatment, survival is much improved but the death rate remains significant,with the trials reporting mortality rates of between 5.5 and 46% (Casadevall & Perfect 1998).

Drug toxicities are frequent, occurring in up to 60% of patients. The patient's underlying disease is probably the single most important factor determining eventual outcome. Those with malignancy have a poorer prognosis than AIDS patients in industrialized countries because of their older age and the relative difficulty in controlling their underlying disease. There has been inconsistency in the factors identified as poor prognostic indicators, but those thought most likely to predict treatment failure are a high initial CSF opening pressure, high CSF cryptococcal antigen and abnormal mental status at presentation (Casadevall & Perfect 1998).

AIM AND OBJECTIVES

Aim:

To compare the efficacy of 3 weeks Amphotericin therapy vs 2 weeks Amphotericin therapy in HIV positive cryptococcal meningitis patients & also ascertain the impact of both on CSF parameters.

Objectives:

- To diagnose the Cyptococcal meningitis by detection of Cryptococcal antigen in CSF,india ink preparation and culture.
- To treat the Cryptococcal meningitis proven HIV positive patient with 3 weeks Amphotericin regimen
- To compare the impact of Amphotericin therapy at the end of second week and third week by repeating india ink preparation,culture and other CSF parameters.

MATERIALS AND METHODS

Prospective observational study; sample size: 100

Inclusion criteria:

- Age ≥ 18 yrs
- Both the genders
- Patient/relative willing to give informed consent
- Clinically suspected case of meningitis
- Global cerebral syndrome with proven case of Cryptococcal meningitis

Exclusion criteria:

- Already treated or under the treatment for cryptococcal meningitis
- Any contraindication for performing lumbar puncture
- Partially treated & relapsing cases
- Patient /relative not willing to give informed consent
- Age <18 & >60 years

Methodology:

After the initial case history and detailed examination all HIV reactive individuals suspected of having meningitis/ meningoencephalitis are to be subjected to CSF analysis (including India ink preparation, culture and antigen detection) ,CD4 counts and imaging studies. The positive cases have to be followed up with repeat CSF analysis at 2^{nd} and 3^{rd} week after a regimen of anti fungal therapy. So, by comparing the CSF parameters vise; India ink preparation, culture, cell counts, protein, sugar at the end of 2^{nd} and 3^{rd} week after Amphotericin treatment, the efficacy of duration of treatment and outcome can be ascertained.

OBSERVATION AND RESULTS

INCIDENCE OF CRYPTOCOCCAL MENINGITIS IN 100 HIV PATIENTS

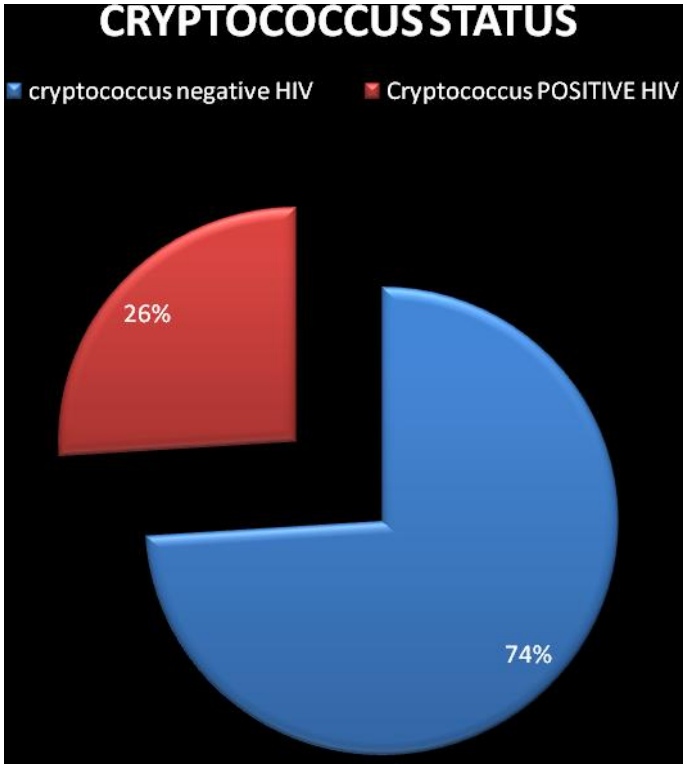


TABLE 1

AGE

SAMPLE	AGE IN YEARS	
	MEAN	SD
CRYPTOCOCCAL NEGATIVE PATIENTS (n=74)	36.2	5.2
CRYPTOCOCCAL POSITIVE PATIENTS (n=26)	34.5	5.0

In our study population, mean age of patients with cryptococcal meningitis were 34.5, whereas in cryptococcal negative HIV patients it was 36.5 years.

TABLE-2

SEX

SEX	CRYPTOCOCCAL NEGATIVE PATIENTS (n=74)	CRYPTOCOCCAL POSITIVE PATIENTS (n=26)	TOTAL
MALE	55	19	74
FEMALE	19	7	26

In total no of HIV patients there are about 75% were male and about 25% were female, in cryptococcal meningitis group 73% were males and 27% were females.

TABLE-3

MARITAL STATUS

MARITAL STATUS	CRYPTOCOCCAL NEGATIVE PATIENTS (n=74)	CRYPTOCOCCAL POSITIVE PATIENTS (n=26)	TOTAL
MARRIED	64	25	89
UNMARRIED	10	1	11

In total no of HIV patients there are about 90% were married and about 10% were unmarried, in cryptococcal meningitis group 96% were married and 4% were unmarried.

TABLE-4

EDUCATIONAL STATUS

EDUCATION	CRYPTOCOCCAL NEGATIVE PATIENTS (n=74)	CRYPTOCOCCAL POSITIVE PATIENTS (n=26)	TOTAL
UNEDUCATED	7	3	10
PRIMARY	45	15	60
SECONDARY	14	5	19
DEGREE	8	3	11

Most number of patients completed only their primary level of education in both groups.

TABLE-5

PROMISCOUS SEX

PROMISCOUS SEX	CRYPTOCOCCAL NEGATIVE PATIENTS (n=74)	CRYPTOCOCCAL POSITIVE PATIENTS (n=26)	TOTAL
YES	6	2	8
NO	68	24	92

Ninety two percent of total HIV patients not maintained their sexual promiscuous like that patients with cryptococcal meningitis not maintained their sexual promiscuous.

TABLE-6

OCCUPATION

OCCUPATION	CRYPTOCOCCAL NEGATIVE PATIENTS (n=74)	CRYPTOCOCCAL POSITIVE PATIENTS (n=26)	TOTAL
UNEMPLOYED	9	3	12
LABOUR	33	7	40
FARMER	8	2	10
PRIVATE	8	2	10
PROFESSIONAL	3	3	6
HOUSEWIFE	2	0	2
DRIVER	11	9	20

From the above table most number of HIV positive cryptococcal negative patients was engaged in labor works, whereas in patients with cryptococcal meningitis most of them were drivers.

TABLE-7

INITIAL CLINICAL PRESENTATION

CLINICAL PRESENTATION	TOTAL (n=100)	CRYPTOCOCCAL POSITIVE PATIENTS (n=26)
FEVER	89	25
HEADACHE	96	24
MALAISE	39	14
VOMITTING	42	10
NECK STIFFNESS	25	10
ALTERED SENSORIUM	28	8
SEIZURE	14	2
COUGH	4	2
DYSPHAGIA	10	1
FOCAL NEUROLOGICAL DEFICITS	16	1
BLURRING OF VISION	2	1

Headache (96% of patients) is the most common presentation in total no of HIV patients, whereas fever and headache (was the most common presentations in cryptococcal meningitis patients.

TABLE-8

PRE EXIXSTING DISEASES

PRE EXISTING DISEASES	CRYPTOCOCCAL NEGATIVE PATIENTS (n=74)	CRYPTOCOCCAL POSITIVE PATIENTS (n=26)	TOTAL
TB	24	4	28
ON ATT	15	2	17

TB was the pre existing disease (28% of patients) in both cryptococcal negative and positive HIV patients; it was present 4 out of 26 patients with cryptococcal meningitis, out of total TB patients only 17 of them on ATT.

TABLE-9

DISEASE PATTERN OF HIV REACTIVE INDIVIDUALS SUSPECTED OF HAVING MENINGITIS/MENINGOENCEPHALITIS

DISEASES	TOTAL NO OF PATIENTS
CRYPTOCOCCAL MENINGITIS	26
TB MENINGITIS	7
TOXOPLASMOSIS	4
CNS LYMPHOMA	2

In 100 HIV reactive individuals with features suggestive of meningial involvement, 26 patients were cryptococcal meninigitis, 7 patients had TB meningitis, 4 patients had Toxoplasmosis and 2 patients had CNS Lymphoma.

TABLE-10

SAMPLE	CD4 COUNT		SIGNIFICANCE
	MEAN	SD	
CRYPTOCOCCAL NEGATIVE PATIENTS (n=74)	76.6	42.27	T=2.2715 P=0.025 SIGNIFICANT
CRYPTOCOCCAL POSITIVE PATIENTS (n=26)	56.42	27.15	

CD4 COUNT

In our study, mean CD4 level in patients with cryptococcal meningitis was 56.42, and in cryptococcal negative HIV patients it was 76.6, and this difference in CD4 count was found to be statistically significant (p=0.025)

TABLE-11

INITIAL CSF PARAMETER

INITIAL CSF PARAMETER	CRYPTOCOCCAL NEGATIVE PATIENTS (n=74)		CRYPTOCOCCAL POSITIVE PATIENTS (n=26)		SIGNIFICANCE
	MEAN	SD	MEAN	SD	
CSF PROTEIN	145.7	92.9	150.84	47.3	T=0.2699 P=0.7829
CSF SUGAR	37.9	17.1	15.61	8.7	T=6.321 P=0.000 SIGNIFICANT
CSF CELL COUNT	40.02	62.4	32.30	18.4	T=0.6189 P=0.53

Initial CSF routine characters in both groups were;

- Mean CSF protein was 150.84 and 145.7 in cryptococcal positive and negative patients respectively,
- Mean sugar value was 15.61 in cryptococcal positive patients and 37.9 in cryptococcal negative patients and this different was found statistically significant (p=0.0000),
- Mean CSF cell count was 32.3 and 40 in cryptococcal positive and negative patients respectively.

TABLE-12

CSF PARAMETER OF SECOND AND THIRD WEEK AFTER AMPHOTERICIN TREATMENT

CSF PARAMETER	SECOND WEEK		THIRD WEEK		SIGNIFICANCE
	MEAN	SD	MEAN	SD	
CSF PROTEIN	102.04	29.5	62.6	20.8	T=5.5772 P=0.000 SIGNIFICANT
CSF SUGAR	32.5	11.4	55	10.3	T=7.487 P=0.000 SIGNIFICANT
CSF CELL COUNT	13.9	12	2	4.4	T=4.769 P=0.000 SIGNIFICANT

- Mean CSF protein level at the end of 14th day of Amphotericin B treatment was 102 and it became further reduced to 62.6 after one week extended Amphotericin B treatment, and this improvement in CSF protein level was statistically significant (p=0.00).
- Mean CSF sugar level at the end of 14th day of Amphotericin B treatment was 32.5 and it became further increased to 55 after one week extended Amphotericin B treatment, and this improvement in CSF sugar level was statistically significant (p=0.00).
- Mean CSF cell count level at the end of 14th day of Amphotericin B treatment was 13.9, and it became further reduced to 2 after one week extended Amphotericin B treatment, and this improvement in CSF cell count level was statistically significant (p=0.00).

TABLE-13

INDIA INK AND CULTURE ON SDA

CSF PARAMETER	SECOND WEEK		THIRD WEEK		SIGNIFICANCE
	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE	
INDIA INK FOR CRYPTOCOCCI	22	4	5	21	Chi square=22.26 P=0.000 SIGNIFICANT
CULTURE IN SDA	19	7	3	23	Chi square-17.72 P=0.000 SIGNIFICANT

CSF became sterile on the 14th day of Amphotericin B in 7 patients (26.9%) while 19 patients (73.1%) had positive CSF culture, India ink became negative on the 14th of treatment in 4 patients (15.3%) while had still positive in 22 patients (84.6%), and all these patients were treated with an extended course of Amphotericin B by one more week.

At the third week about 23 out of 26 patients CSF became sterile, 21 out of 26 patients shown negative in CSF India ink preparation, these differences were statistically significant.

TABLE-14

CLINICAL IMPROVEMENT OF SECOND AND THIRD WEEK AFTER AMPHOTERICIN TREATMENT

CLINICAL IMPROVEMENT	SECOND WEEK		THIRD WEEK		SIGNIFICANCE
	IMPROVED	NOT IMPROVED	IMPROVED	NOT IMPROVED	
TOTAL NO OF PATIENTS	5	21	22	4	Chi square-22.26 P=0.000 SIGNIFICANT

Only 5 patients (19%) got improved clinically on 14^{th} day of treatment, but after extension of one more week Amphotericin B treatment 22 patients improved clinically, 4 patients still not improved even after 3 weeks treatment.

FIGURE-1

CSF PROTEIN LEVEL 2ND AND 3RD WEEK FOLLOWING AMPHOTERICIN B TREATMENT

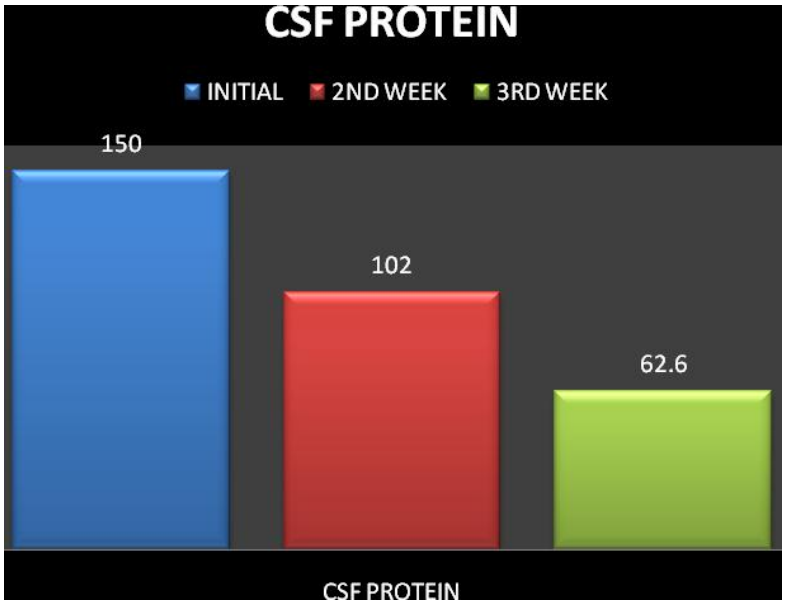


FIGURE-2

CSF SUGAR LEVEL 2ND AND 3RD WEEK FOLLOWING AMPHOTERICIN B TREATMENT

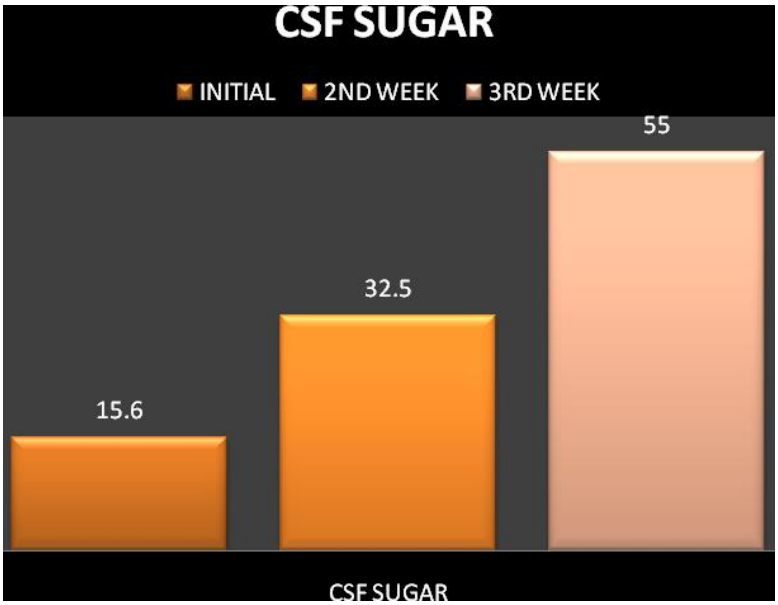


FIGURE-3

CSF CELL COUNT LEVEL 2ND AND 3RD WEEK FOLLOWING AMPHOTERICIN B TREATMENT

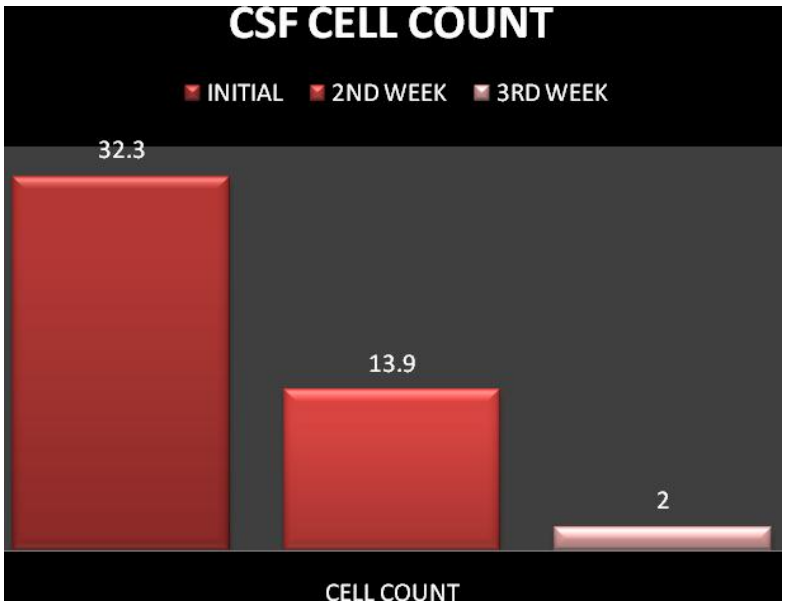


FIGURE-4

NEGATIVE FOR CRYPTOCOCCI IN INDIA INK AND CULTURE IN SDA AT 2ND AND 3RD WEEK FOLLOWING AMPHOTERICIN TREATMENT

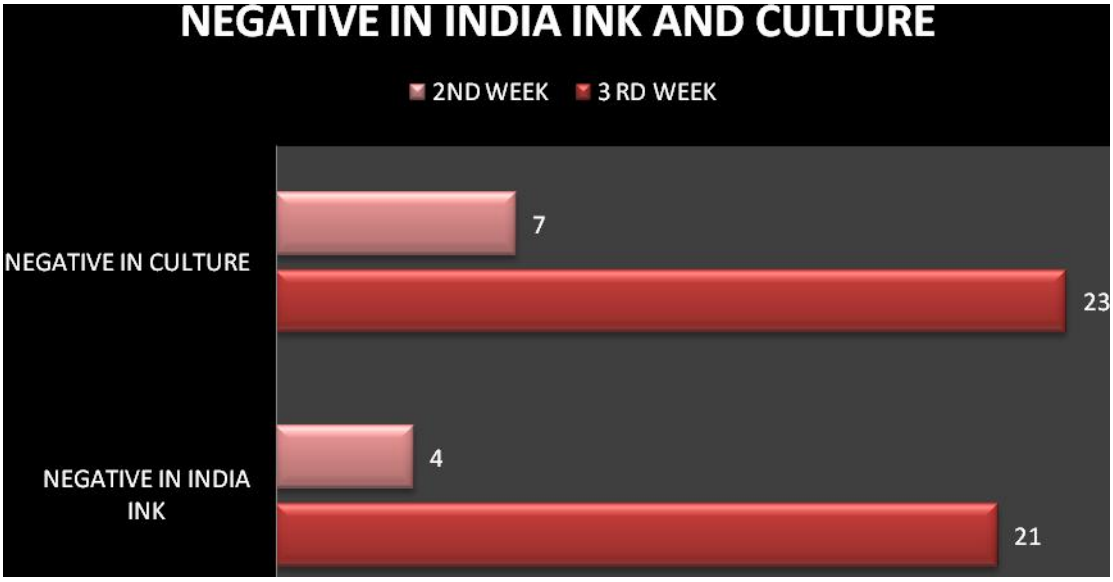
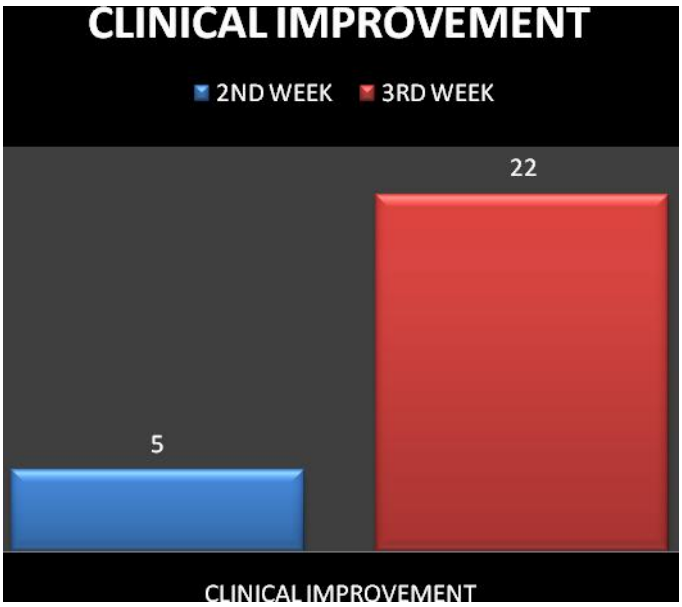


FIGURE-5

CLINICAL IMPROVEMENT AT 2ND AND 3RD WEEK FOLLOWING AMPHOTERICIN TREATMENT



DISCUSSION

In this study,out of the 100 seropositive patients, 26 had cryptococcal meningitis (26%), 7 had TB meningitis, 4 had toxoplasmosis and 2 had CNS lymphoma, The incidence of neurological manifestations in HIV positive patients according to snider et al was 31% and levy et al was 39%. In India Gupta et al 41 found an incidence of 25.75% in his study.

AGE

Mean age of the patients in this study were in 36.2 years in seropositive non cryptococcal meningitis patients, the mean age of the patients with cryptococcal meningitis were 34.5 years, this is more or less consistent with the a study in university of California and Sanfransisco where it was 37.3 years and 38 respectively.

SEX

Male patients were found to have cryptococcal meningitis more common (73.1%) as against females (26.9%). Mehta et al has reported male predominance with male to female ratio of 12:1. Another study is also consistent with the finding Patel et al found male female ratio was 8:2.

OCCUPATION

High incidence of cryptococcal meningitis was noted among drivers(34%), followed by daily wage labourers with 26%. Perhaps these patients more

often seek medical help in government hospital and also because HIV infection rate are high in this group of patients.

MODE OF TRANSMISSION

Ninety three percent patients with cryptococcal meningitis had heterosexual behaviour as the risk factor. None of our patients had homosexual relationship. Gupta et al41 found heterosexual relationship in 64.7%, 5.85% in drug abusers and blood transfusion in 14.7%.

PRE-EXISTING INFECTION

Among cryptococcal meningitis patients 4 patients (15.4%) had tuberculosis as pre existing illness. This finding goes accordance with Patel et al where he found that 22% patients had tuberculosis as pre existing illness.

CLINICAL PRESENTATION

FEVER

This was the commonest presentation in cryptococcal meningitis patients 25 out of 26 cryptococcal meningitis patients had suffered from fever.

HEADACHE

This was the commonest presenting symptom in our study. 96 out of the 100 patients suspected to have meningial involvement had headache, 24 out of 26 patients (92.3%) cryptococcal meningitis presented with headache. It is consistent with Patel et al where 96.3 % cryptococcal meningitis presented with headache.

ALTERED SENSORIUM

Thirty percent of the cryptococcal meningitis patients had altered sensorium, whereas in total of 100 HIV patients 28 % of patients had altered sensorium

Altered sensorium as observed in this study was primarily due to a meningial infection, cryptococcal meningitis being most frequent, followed by TB meningitis, Toxoplasmosis and CNS lymphoma. University of California and Sanfransisco data revealed altered sensorium as a manifestation in secondary viral infection. Progressive multifocal leucoencephalopathy, toxoplasmosis, cryptococcosis, HIV dementia and lymphoma.

SEIZURES

In our study, 14 % of patients had seizure episodes the common cause for seizures was neurotuberculosis and Toxoplasmosis. Of the 26 patients of cryptococcal meningitis, 2 patients had seizures (8%). This finding goes against with Patel et al where 33 % of cryptococcal meningitis patients had seizure.

COMPARATIVE TABLE: 1

	Patel et al 2010	This study
No of cryptococcal meningitis	27	26
Headache	26 (96%)	24 (92%)
Fever	18 (66%)	25 (96%)
Seizure	9 (33%)	2 (7%)
Altered sensorium	9 (33%)	8 (30%)
Focal neurological deficits	4 (14%)	1 (3.8%)
Malaise	10 (37%)	14 (53.8%)
Vomiting	21 (77%)	10 (38%)
Neck stiffness	NA	10 (38%)

SEIZURE DISORDERS

Two patients in this study group presented as seizure disorder (6.8%). One patient presented with left focal seizure involving upper limb with secondary generalization and the other patient had generalized tonic clonic seizures.

Approximately half of HIV infected patients with seizures have no definite Identifiable disease of the brain and cerebral HIV infection seems to be the most likely cause of the seizures. It the study by Holtzman et al, HIV encephalopathy was responsible for seizures in 24% of the patients.

CD4 CORRELATION

There were 26 Patients diagnosed to have Cryptococcal Meningitis. The mean CD4 count of patients with Cryptococcal Meningitis in the study group was 56.42 and the mean CD4 count of patients who did not have Cryptococcal Meningitis was 76.6. Statistically significant different of CD4 count was observed between the two groups. (P-0.025).

Myoung-don Oh et al (74) detected that CD4+ lymphocyte counts at presentation were <200/micro L in 27% of the patients with opportunistic infections

SK Sharma et al (5) found that majority of the patients 82.6% had CD4+ counts <200 cells/μL. 46% had CD4+ counts <50 cells/μL.

COMPARATIVE TABLE : 2

	Gupta et al	**Bandyopadhyay et al**	**Our study**
Year of study	1993	2005	2010
Incidence	25%	32.9%	26%
Modes of transmission	Heterosexual - 64.5% I.V Drug abuser - 5.85 % Blood transfusion - 14.7 %	NA	Heterosexual - 100%
Cryptococcal meningitis	8.8%	6.0%	26%
TB Meningitis	58.82%	12.1%	7%
Toxoplasmosis	3.8%	2.5%	4%
CNS Lymphoma	NA	NA	2%

INITIAL CSF PARAMETER

All patients in our study underwent CSF examinations, India ink preparation, CSF Crag and CSF culture. Patients presenting with altered sensorium with focal neurological deficits or intense headache not improving despite lumbar tape and negative fungal growth were subjected to neuroimaging.

Initial CSF routine characters were;

- Mean CSF protein was 150.84 and 145.7 in cryptococcal positive and negative patients respectively,
- Mean sugar value was 15.61 in cryptococcal positive patients and 37.9 in cryptococcal negative patients and this different was found statistically significant (p=0.0000),
- Mean CSF cell count was 32.3 and 40 in cryptococcal positive and negative patients respectively.

CSF finding in our study is contrast to Kumar et al study where elevated protein in 45% of patients, CSF sugar low in 75% of patients, CSF WBC count more than 5 in 55% of patients.

In our study CSF India ink positivity showed in 100% of patients where in Kumar et al 85% of patients, Crag and culture was positive in all patients with cryptococcal meningitis in both studies.

TREATMENT

All cryptococcal meningitis patients (n=26) treated with Amphotericin B 0.7 mg/kg of body wt per day for three weeks used as a induction therapy. Amphotericin B was infused on 5% dextrose over 8 h and the patient received 500 ml of 0.9% normal saline before infusion to reduce Amphotericin related toxicity. In addition to these patients were encouraged to ensure liberal intake of fluids and coconut water and citrus fruit and banana daily. Amphotericin toxicity was monitored with twice weekly creatinine, BUN and K level.

These patients Ca and Mg levels were also checked and corrected if required. Amphotericin treatment was discontinued in patients with rising creatinine level and resumed once creatinine level touches baseline. Fever and chills related to Amphotericin B infusion were treated with Injection Hydrocortisone 50 mg iv sos.

Raised intra cranial pressure was controlled with lumbar tape and mannital.frequency of lumbar tape was guided by patient's clinical symptoms. 15 to 20 ml of CSF was removed at one time to control the raised ICT.

SUCCESSFUL RESPONSE

Treatment response was defined as sterile CSF culture, India ink preparation negativity and improved clinically at day 14. Patients with

persisting positivity in culture, India ink and not improved clinically were continued for one more week and evaluated with repeat CSF analysis. They were then consolidated 400 mg of Flucanazole for 8 weeks and maintained on Flucanazole 200 mg/day.

CSF became sterile on the 14^{th} day of Amphotericin B in 26.9% of the patients while 73.1% had positive CSF culture, India ink became negative on the 14^{th} of treatment in 15.3% of patients while had still positive in 84.6% of patients, mean protein, sugar and cell count on 14^{th} day of treatment were respectively 102, 32.5 and 13.9, and only 5 patients (19%) got improved clinically on 14^{th} day of treatment, all these patients were treated with an extended course of Amphotericin B by one more week.

At the third week about 89% of patients CSF became sterile, 80% of patients shown negative in CSF India ink preparation, 84.6% of patients improved clinically, mean protein, sugar, cell count were respectively 62.6, 55, and 2 at third week following Amphotericin B treatment. These differences were statistically significant.

In one study done at 2006, CSF became sterile on 12^{th} day of Amphotericin B in 55.55% of the patients while 33.33% had positive CSF culture and were treated with an extended course of Amphotericin B by 1 more week. All these patients became sterile on day 19 (Kumar et al).

Hongzhou Lu et al 2005, demonstrated in his study cryptococcal antigen titre decrease after anti fungal therapy. There was remarkable decrease in cryptococcal antigen titre after therapy which was significantly related to CSF leukocyte count, glucose, chloride, fungal smear and fungal culture measurements. The total protein level in CSF decreases after therapy but this different was not statistically significant.

SUMMARY

We carried out a prospective observational study to determine the treatment response rate, tolerability and outcome of patients with cryptococcal meningitis in HIV treated with Amphotericin B. Descriptive statistic was used to analyze the data.

After the initial case history and detailed examination of all HIV reactive individuals suspected of having meningitis/ meningoencephalitis are to be subjected to CSF analysis (including India ink preparation, culture and antigen detection) ,CD4 counts and imaging studies. The positive cases have to be followed up with repeat CSF analysis at 2^{nd} and 3^{rd} week after a regimen of anti fungal therapy. So, by comparing the CSF parameters vise ; India ink preparation, culture on SDA, cell counts, protein, sugar and clinical improvement at the end of 2^{nd} and 3^{rd} week after Amphotericin treatment, the efficacy of duration of treatment and outcome can be ascertained.

A total of 26 patients were diagnosed with cryptococcal meningitis during the study period. Headache and fever was the most common presenting symptom of cryptococcal meningitis in HIV-infected patients, followed by malaise and vomiting. All patients in our study had heterosexual transmission of disease. Tuberculous meningitis, Toxoplasmosis and CNS lymphoma were the other opportunistic infection encountered in our study. There was significant

CD4 count correlation was found between the patients with cryptococcal meningitis and those without cryptococcal meningitis.

Initial CSF routine characters in both groups were; mean CSF protein was 150.84 and 145.7 in cryptococcal positive and negative patients respectively, mean sugar value was 15.61 in cryptococcal positive patients and 37.9 in cryptococcal negative patients and this different was found statistically significant (p=0.0000), mean CSF cell count was 32.3 and 40 in cryptococcal positive and negative patients respectively.

Mean CSF protein level at the end of 14^{th} day of Amphotericin B treatment was 102 and it became further reduced to 62.6 after one week extended Amphotericin B treatment, and this improvement in CSF protein level was statistically significant (p=0.00), mean CSF sugar level at the end of 14^{th} day of Amphotericin B treatment was 32.5 and it became further increased to 55 after one week extended Amphotericin B treatment, and this improvement in CSF sugar level was statistically significant (p=0.00), mean CSF cell count level at the end of 14^{th} day of Amphotericin B treatment was 13.9, and it became further reduced to 2 after one week extended Amphotericin B treatment, and this improvement in CSF cell count level was statistically significant (p=0.00).

CSF became sterile on the 14^{th} day of Amphotericin B in 7 patients (26.9%) while 19 patients (73.1%) had positive CSF culture, India ink became

negative on the 14th of treatment in 4 patients (15.3%) while had still positive in 22 patients (84.6%), and all these patients were treated with an extended course of Amphotericin B by one more week.

At the third week about 23 out of 26 patients CSF became sterile, 21 out of 26 patients shown negative in CSF India ink preparation, these differences were statistically significant.

Only 5 patients (19%) got improved clinically on 14th day of treatment, but after extension of one more week Amphotericin B treatment 22 patients improved clinically, 4 patients still not improved even after 3 weeks treatment.

CONCLUSIONS

- Incidence of Cryptococcal meningitis in HIV infection in our study was 26%.
- In our study male out number female in both cryptococcal negative (75% versus 25%) and positive (96% versus 4%) HIV patients.
- Headache and fever were the two common symptoms observed in this study.
- Ninety three patients in our study had heterosexual transmission of disease.
- Tuberculous meningitis, Toxoplasmosis and CNS lymphoma were the other opportunistic infection encountered in our study.
- Significant CD4 count correlation was found between the patients with cryptococcal meningitis and those without cryptococcal meningitis.
- We found that the recommended two weeks induction treatment with Amphotericin B mono therapy for HIV patients with cryptococcal meningitis in resource limited settings may be sub optimal for at least two third of patients.
- Extending the therapy to three weeks is likely to results in sterilization of the CSF in majority of these patients.

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Proforma:

1. Name:
2. Age:
3. Sex:
4. Marital status:
5. Education:
6. Occupation:
7. Address:
8. Height:
9. Weight:
10. HIV detection:
    - When detected? :
    - Where detected?:
    - HAART therapy:
11. Clinical presentation:
12. Antecedent symptoms:
13. Drugs:
14. Liver/lung kidney/heart disease:
15. Hypertension/diabetes/hyperlipidemia:
16. Promiscous sex:
17. Smoking/alcohol:
18. General examination:
19. Vital signs:
20. CNS:
21. CVS
22. RS
23. P/A:

Investigations:

1.urine r/e:

- Albumin
- Sugar
- Deposits

2.RFT:

Sugar

Urea

Creatinine

3.CBC:

4.CXR:

5.ECG:

6.Brain imaging:

7.CD4 count:

8.CSF analysis:

Appearance:

Protein:

Sugar:

Cell count:

India ink preparation:

Culture in SDA:

Crytococcal antigen:

9.others:

CONSENT FORM

I AGREE TO PARTICIPATE IN THE STUDY TITLED"COMPARATIVE STUDY OF THE EFFICACY OF 3 WEEKS VS 2 WEEKS AMPHOTERICN THERAPY IN HIV POSITIVE CRYPTOCOCCAL MENINGITIS PATIENTS & ALO ASCERTAIN THE IMPACT OF BOTH ON CSF PARAMETERS".

I CONFIRM THAT I HAVE BEEN TOLD ABOUT THIS STUDY IN MY MOTHER TONGUE AND HAVE HAD THE OPPORTUNITY TO ASK QUESTIONS.

I UNDERSTAND THAT MY PARTICIPATION IS VOLUNTARY AND I MAY REFUSE TO PARTICIPATE AT ANY TIME WITHOUT GIVING ANY REASON AND WITHOUT AFFECTING MY BENEFITS.

I AGREE NOT TO RESTRICT THE USE OF ANY DATA /RESULTS THAT MAY ARISE FROM THE STUDY.

RELATIVE:

SIGNATURE OF THE RELATIVE INVESTIGATOR

SIGNATURE OF THE PATIENT

S.NO	AGE	SEX	EDUCATION	OCCUPATION	MARITAL	HIV STATUS	DURATION OF HIV IN MONTHS	DURATION OF HAART IN MONTH	HEAD ACHE	FEVER	MALAISE	VOMITTING	NECK STIFFNESS	ALTERED MENTATION	SEIZURE	OTHER PRESENTATION	DRUGS	HT	DM	CAD	CKD	TB	PROMISCOUS SEX	SUBSTANCE ABUSE	CXR	BRAIN IMAGING	CD4	CSF APPEARENCE1	CSFPROTEIN1	CSF SUGAR1	CSF CELLCOUNT1	INDIA INK1	CULTURE SDA1	CRAG1	CRYPTO STATUS1	OTHERS	CSF APPEARENCE2	CSFPROTEIN2	CSF SUGAR2	CSF CELLCOUNT2	INDIA INK2	CULTURE SDA2	CLINICAL IMPROVEMENT2	CSF APPEARENCE3	CSFPROTEIN3	CSF SUGAR3	CSF CELLCOUNT3	INDIA INK3	CULTURE SDA3	CLINICAL IMPROVEMENT3
1	42	M	3	6	1	1	3	1	1	1	1	1	2	1	2	1	2	2	2	2	2	2	2	1	0	0	46	1	69	32	40	1	1	1	1	0	1	50	50	2	1	1	2	1	30	60	0	2	2	1
2	36	M	1	3	1	1	1	1	1	1	1	1	1	1	2	0	ATT	2	2	2	2	1	2	1	PT	0	8	1	116	70	0	2	2	2	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	30	M	1	9	1	1	36	0	1	1	1	1	2	1	2	0	ATT	2	2	2	2	1	2	1	PT	0	9	1	100	38	60	1	1	1	1	0	1	68	25	32	1	2	1	1	58	60	0	2	2	1
4	40	M	0	2	1	1	4	0	1	1	2	2	1	2	2	2	ATT	2	2	2	2	1	2	1	PT	0	114	1	219	74	68	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	40	M	1	3	1	1	8	1	1	2	1	1	2	1	2	0	ATT	2	2	2	2	1	2	1	PT	0	95	1	240	40	24	2	2	2	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6	40	M	1	2	1	1	12	2	1	1	2	2	2	2	2	3	ATT	2	2	2	2	1	2	1	PT	0	17	1	50	62	0	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7	36	M	1	2	1	1	6	3	1	1	1	1	2	2	1	0	2	2	2	2	2	2	2	1	0	0	43	1	126	25	42	1	1	1	1	0	1	102	30	20	1	1	2	1	60	65	0	2	2	1
8	35	M	1	2	1	1	3	1	1	1	2	1	1	1	2	0	ATT	2	2	2	2	1	2	1	PT	0	179	1	525	43	120	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9	37	M	0	9	1	1	12	12	1	2	2	1	2	2	2	0	ATT	2	2	2	2	1	2	1	PT	0	42	1	114	10	80	1	1	1	1	0	1	130	31	8	1	2	2	1	60	50	0	2	2	1
10	31	M	1	2	1	1	12	12	1	1	2	1	2	1	2	3	0	2	2	2	2	1	2	1	PT	0	69	1	352	16	84	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11	29	M	3	4	2	1	36	6	1	2	2	1	2	2	2	0	0	2	2	2	2	2	2	2	0	1	66	1	122	35	18	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
12	41	M	2	2	1	1	120	24	1	1	2	2	2	2	2	3	0	2	2	2	2	2	2	1	0	0	18	1	107	55	0	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
13	27	M	1	2	2	1	1	1	1	1	2	2	2	2	2	0	ATT	2	2	2	2	1	2	1	0	0	164	1	29	57	20	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
14	35	M	1	9	1	1	12	6	1	1	2	1	2	2	2	0	ATT	2	2	2	2	1	2	1	PT	0	107	1	104	10	8	1	1	1	1	0	1	98	30	4	1	1	2	1	65	60	0	2	2	1
15	33	M	0	2	1	1	12	1	1	1	2	1	2	2	1	4	0	2	2	2	2	2	2	1	PT	0	23	1	148	10	26	1	1	1	1	0	1	60	40	22	1	2	2	1	39	48	0	2	2	1
16	28	M	0	2	1	1	6	2	1	1	1	1	2	2	2	0	0	2	2	2	2	2	2	2	0	0	50	1	242	21	72	1	1	1	1	0	1	149	30	50	1	1	2	1	60	65	0	2	2	1
17	30	M	1	9	1	1	10	4	1	1	2	2	2	2	2	0	0	2	2	2	2	2	2	1	0	0	60	1	150	25	32	1	1	1	1	0	1	58	25	30	1	2	1	1	45	45	0	2	2	1
18	48	F	1	2	1	1	12	5	1	1	2	2	2	2	2	0	0	2	2	2	2	2	2	2	0	0	104	1	123	45	18	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
19	42	M	2	3	1	1	36	24	1	2	1	1	2	2	2	0	0	2	2	2	2	2	2	1	0	0	98	1	158	32	24	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
20	36	M	2	9	1	1	20	12	1	1	2	2	1	1	2	0	0	2	2	2	2	2	2	1	0	0	42	1	256	10	56	1	1	1	1	0	1	180	20	40	1	1	2	1	100	38	16	1	1	2
21	28	M	3	4	2	1	12	0	1	1	1	2	2	2	2	0	0	2	2	2	2	2	2	1	0	0	106	1	128	46	8	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
22	34	M	1	2	1	1	18	10	1	1	1	2	2	1	2	0	0	2	2	2	2	2	2	1	0	0	40	1	190	8	30	1	1	1	1	0	1	100	20	12	1	1	2	1	60	65	0	2	2	1
23	35	M	1	9	1	1	18	6	1	1	2	2	2	2	2	0	0	2	2	2	2	2	2	1	0	0	98	1	106	40	8	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
24	40	M	2	4	1	1	10	4	1	1	1	1	2	2	2	0	0	2	2	2	2	2	2	1	0	0	104	1	116	40	13	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
25	45	M	1	2	1	1	8	3	1	1	1	2	2	2	2	0	0	2	2	2	2	2	2	1	0	0	96	1	136	30	16	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
26	29	M	3	6	2	1	6	0	1	1	2	2	1	2	2	2	0	2	2	2	2	2	2	1	0	0	86	1	156	10	30	1	1	1	1	0	1	96	26	13	1	1	2	1	60	65	0	2	2	1
27	40	M	1	3	1	1	30	18	1	1	2	2	2	2	1	3	0	2	2	2	2	2	2	1	0	0	56	1	120	30	12	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
28	27	M	2	9	1	1	16	6	1	1	1	1	2	2	2	0	0	2	2	2	2	2	2	1	0	0	56	1	106	36	13	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
29	36	F	1	1	1	1	16	12	1	1	1	2	1	2	2	0	0	2	2	2	2	2	2	2	0	0	100	1	186	10	40	1	1	1	1	0	1	98	26	18	1	1	2	1	48	60	0	2	2	1
30	45	F	1	8	1	1	13	3	1	2	2	2	2	1	1	3	0	2	2	2	2	2	2	2	0	2	50	1	90	40	0	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
31	38	F	1	1	1	1	18	16	1	1	2	2	2	2	2	0	0	2	2	2	2	2	2	2	0	0	88	1	144	12	18	1	1	1	1	0	1	124	16	16	1	1	2	1	100	46	12	1	2	1
32	40	M	0	2	1	1	4	0	1	1	2	2	1	2	2	2	0	2	2	2	2	1	2	1	PT	0	114	1	219	74	68	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
33	42	M	3	6	1	1	3	1	1	1	1	1	2	1	2	1	0	2	2	2	2	2	2	1	0	0	46	1	69	32	40	1	1	1	1	0	1	50	50	2	1	1	2	1	30	60	0	2	2	1
34	36	M	1	2	1	1	12	10	1	2	2	1	2	1	1	3	0	2	2	2	2	2	2	1	0	3	50	1	150	38	28	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
35	41	M	2	2	1	1	120	24	1	1	2	2	2	2	2	3	0	2	2	2	2	2	2	1	0	0	18	1	107	55	0	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
36	27	M	1	2	2	1	1	1	1	1	2	2	2	2	2	0	ATT	2	2	2	2	1	2	1	0	0	164	1	29	57	20	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

S.NO	AGE	SEX	EDUCATION	OCCUPATION	MARITAL	HIV STATUS	DURATION OF HIV IN MONTHS	DURATION OF HAART IN MONTH	HEAD ACHE	FEVER	MALAISE	VOMITTING	NECK STIFFNESS	ALTERED MENTATION	SEIZURE	OTHER PRESENTATION	DRUGS	HT	DM	CAD	CKD	TB	PROMISCOUS SEX	SUBSTANCE ABUSE	CXR	BRAIN IMAGING	CD4	CSF APPEARENCE1	CSFPROTEIN1	CSF SUGAR1	CSF CELLCOUNT1	INDIA INK1	CULTURE SDA1	CRAG1	CRYPTO STATUS1	OTHERS	CSF APPEARENCE2	CSFPROTEIN2	CSF SUGAR2	CSF CELLCOUNT2	INDIA INK2	CULTURE SDA2	CLINICAL IMPROVEMENT2	CSF APPEARENCE3	CSFPROTEIN3	CSF SUGAR3	CSF CELLCOUNT3	INDIA INK3	CULTURE SDA3	CLINICAL IMPROVEMENT3
37	35	M	1	9	1	1	12	6	1	1	2	1	2	2	2	0	0	2	2	2	2	1	2	1	PT	0	107	1	104	10	8	1	1	1	1	0	1	98	30	4	1	1	2	1	65	60	0	2	2	1
38	32	F	1	2	1	1	10	6	1	1	2	2	1	1	2	0	0	2	2	2	2	2	2	2	0	0	46	1	196	10	30	1	1	1	1	0	1	130	30	20	1	1	2	1	98	36	8	1	1	2
39	50	F	2	4	1	1	24	12	1	1	1	2	2	2	2	0	0	2	2	2	2	2	2	1	0	0	24	1	106	10	18	1	1	1	1	0	1	96	40	8	1	2	2	1	60	65	0	2	2	1
40	30	F	1	9	1	1	10	6	1	1	2	2	1	2	2	0	0	2	2	2	2	2	2	1	0	0	40	1	150	10	18	1	1	1	1	0	1	106	36	18	1	1	1	1	50	60	0	2	2	1
41	38	M	2	3	1	1	6	3	2	1	1	2	1	2	2	0	0	2	2	2	2	2	2	1	0	0	66	1	182	19	13	1	1	1	1	0	1	106	20	8	1	1	2	1	70	50	0	2	2	1
42	38	M	2	9	1	1	27	17	2	1	1	1	2	2	2	2	0	2	2	2	2	2	2	1	0	0	98	1	98	36	8	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
43	39	M	1	2	1	1	60	24	1	1	2	2	2	1	1	3	0	2	2	2	2	2	2	1	0	0	48	1	98	36	6	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
44	44	F	1	1	1	1	24	18	1	1	2	2	2	2	2	2	0	2	2	2	2	2	2	2	0	0	104	1	98	40	13	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
45	36	M	1	1	1	1	10	1	1	1	2	1	1	2	2	0	0	2	2	2	2	2	2	1	PT	0	60	1	286	30	255	2	2	2	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
46	40	F	1	1	1	1	36	30	1	1	2	1	1	2	1	0	0	2	2	2	2	2	2	2	PT	0	48	1	98	38	8	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
47	30	M	3	4	2	1	3	0	1	1	2	2	2	2	2	0	0	2	2	2	2	2	2	2	0	0	108	1	98	35	8	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
48	34	M	1	2	1	1	3	0	1	1	1	2	2	2	2	0	0	2	2	2	2	2	2	1	0	0	98	1	86	24	0	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
49	41	F	1	1	1	1	24	14	1	1	2	2	2	2	2	0	ATT	2	2	2	2	1	2	2	PT	0	60	1	180	40	250	2	2	2	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
50	45	F	1	8	1	1	13	3	1	2	2	2	2	1	1	3	0	2	2	2	2	2	2	2	0	2	50	1	90	40	0	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
51	38	F	1	1	1	1	18	16	1	1	2	2	2	2	2	0	0	2	2	2	2	2	2	2	0	0	88	1	144	12	18	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
52	40	M	0	2	1	1	4	0	1	1	2	2	1	2	2	2	ATT	2	2	2	2	1	2	1	PT	0	114	1	219	74	68	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
53	42	M	3	6	1	1	3	1	1	1	1	1	2	1	2	1	2	2	2	2	2	2	2	1	0	0	46	1	69	32	40	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
54	36	M	1	2	1	1	12	10	1	2	2	1	2	1	1	3	0	2	2	2	2	2	2	1	0	3	50	1	150	38	28	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
55	41	M	2	2	1	1	120	24	1	1	2	2	2	2	2	3	0	2	2	2	2	2	2	1	0	0	18	1	107	55	0	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
56	27	M	1	2	2	1	1	1	1	1	2	2	2	2	2	0	ATT	2	2	2	2	1	2	1	0	0	164	1	29	57	20	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
57	35	M	1	9	1	1	12	6	1	1	2	1	2	2	2	0	ATT	2	2	2	2	1	2	1	PT	0	107	1	104	10	8	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
58	32	F	1	2	1	1	10	6	1	1	2	2	1	1	2	0	0	2	2	2	2	2	2	2	0	0	46	1	196	10	30	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
59	50	F	2	4	1	1	24	12	1	1	1	2	2	2	2	0	0	2	2	2	2	2	2	1	0	0	24	1	106	10	18	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
60	42	M	3	6	1	1	3	1	1	1	1	1	2	1	2	1	2	2	2	2	2	2	2	1	0	0	46	1	69	32	40	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
61	36	M	1	3	1	1	1	1	1	1	1	1	1	1	2	0	0	2	2	2	2	1	2	1	0	0	8	1	116	70	0	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
62	30	M	1	9	1	1	36	0	1	1	1	1	2	1	2	0	0	2	2	2	2	1	2	1	PT	0	9	1	100	38	60	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
63	40	M	0	2	1	1	4	0	1	1	2	2	1	2	2	2	0	2	2	2	2	1	2	1	0	0	114	1	219	74	68	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
64	40	M	1	3	1	1	8	1	1	2	1	1	2	1	2	0	0	2	2	2	2	1	2	1	0	0	95	1	240	40	226	2	2	2	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
65	40	M	1	2	1	1	12	2	1	1	2	2	2	2	2	3	ATT	2	2	2	2	1	2	1	PT	0	17	1	50	62	0	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
66	36	M	1	2	1	1	6	3	1	1	1	1	2	2	1	0	2	2	2	2	2	2	2	1	0	0	43	1	126	25	42	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
67	35	M	1	2	1	1	3	1	1	1	2	1	1	1	2	0	0	2	2	2	2	1	2	1	0	0	179	1	525	43	120	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
68	37	M	0	9	1	1	12	12	1	2	2	1	2	2	2	0	0	2	2	2	2	1	2	1	0	0	42	1	114	10	80	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
69	31	M	1	2	1	1	12	12	1	1	2	1	2	1	2	3	0	2	2	2	2	1	2	1	PT	0	69	1	352	16	84	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
70	29	M	1	2	1	1	0	0	1	1	1	1	2	2	2	0	0	2	2	2	2	2	2	2	0	0	66	1	160	10	28	1	1	1	1	0	1	112	20	18	1	1	2	1	98	35	8	1	2	2
71	41	M	2	2	1	1	120	24	1	1	2	2	2	2	2	3	0	2	2	2	2	2	2	1	0	0	18	1	107	55	0	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
72	27	M	1	2	2	1	1	1	1	1	2	2	2	2	2	0	0	2	2	2	2	1	2	1	0	0	164	1	29	57	20	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

S.NO	AGE	SEX	EDUCATION	OCCUPATION	MARITAL	HIV STATUS	DURATION OF HIV IN MONTHS	DURATION OF HAART IN MONTH	HEAD ACHE	FEVER	MALAISE	VOMITTING	NECK STIFFNESS	ALTERED MENTATION	SEIZURE	OTHER PRESENTATION	DRUGS	HT	DM	CAD	CKD	TB	PROMISCOUS SEX	SUBSTANCE ABUSE	CXR	BRAIN IMAGING	CD4	CSF APPEARENCE1	CSFPROTEIN1	CSF SUGAR1	CSF CELLCOUNT1	INDIA INK1	CULTURE SDA1	CRAG1	CRYPTO STATUS1	OTHERS	CSF APPEARENCE2	CSFPROTEIN2	CSF SUGAR2	CSF CELLCOUNT2	INDIA INK2	CULTURE SDA2	CLINICAL IMPROVEMENT2	CSF APPEARENCE3	CSFPROTEIN3	CSF SUGAR3	CSF CELLCOUNT3	INDIA INK3	CULTURE SDA3	CLINICAL IMPROVEMENT3
73	35	M	1	9	1	1	12	6	1	1	2	1	2	2	2	0	0	2	2	2	2	1	2	1	0	0	107	1	104	10	8	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
74	33	M	0	2	1	1	12	1	1	1	2	1	2	2	1	4	0	2	2	2	2	2	2	1	PT	0	23	1	148	10	26	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
75	28	M	0	2	1	1	6	2	1	1	1	1	2	2	2	0	0	2	2	2	2	2	2	2	0	0	50	1	242	21	72	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
76	30	M	1	9	1	1		0	1	1	1	2	2	1	2	0	0	2	2	2	2	2	2	1	0	0	60	1	150	25	32	1	1	1	1	0	1	106	30	10	1	1	2	1	45	66	0	2	2	1
77	48	F	1	2	1	1	12	5	1	1	2	2	2	2	2	0	0	2	2	2	2	2	2	2	0	0	104	1	123	45	18	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
78	42	M	2	3	1	1	36	24	1	2	1	1	2	2	2	0	0	2	2	2	2	2	2	1	0	0	98	1	158	32	24	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
79	36	M	2	9	1	1	20	12	1	1	2	2	1	1	2	0	0	2	2	2	2	2	2	1	0	0	42	1	256	10	56	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
80	28	M	3	4	2	1	12	0	1	1	1	2	2	2	2	0	0	2	2	2	2	2	2	1	0	0	106	1	128	46	8	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
81	34	M	1	2	1	1	18	10	1	1	1	2	2	1	2	0	0	2	2	2	2	2	2	1	0	0	40	1	190	8	30	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
82	35	M	1	9	1	1	18	6	1	1	2	2	2	2	2	0	0	2	2	2	2	2	2	1	0	0	98	1	106	40	8	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
83	40	M	2	4	1	1	10	4	1	1	1	1	2	2	2	0	0	2	2	2	2	2	2	1	0	0	104	1	116	40	13	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
84	45	M	1	2	1	1	8	3	1	1	1	2	2	2	2	0	0	2	2	2	2	2	2	1	0	0	96	1	136	30	16	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
85	29	M	3	6	2	1	6	0	1	1	2	2	1	2	2	2	0	2	2	2	2	2	2	1	0	0	86	1	156	10	30	2	2	2	2	0	1	96	26	13	1	1	2	1	60	65	0	2	2	1
86	40	M	1	3	1	1	30	18	1	1	2	2	2	2	1	3	0	2	2	2	2	2	2	1	0	3	56	1	120	30	12	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
87	27	M	2	9	1	1	16	6	1	1	1	1	2	2	2	0	0	2	2	2	2	2	2	1	0	0	56	1	106	36	13	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
88	36	F	1	1	1	1	16	12	1	1	1	2	1	2	2	0	0	2	2	2	2	2	2	2	0	0	100	1	186	10	40	1	1	1	1	0	1	98	26	18	1	1	2	1	48	60	0	2	2	1
89	32	F	1	2	1	1	10	6	1	1	2	2	1	1	2	0	0	2	2	2	2	2	2	2	0	0	46	1	196	10	30	1	1	1	1	0	1	130	30	20	1	1	2	1	98	36	8	1	1	2
90	50	F	2	4	1	1	24	12	1	1	1	2	2	2	2	0	0	2	2	2	2	2	2	1	0	0	24	1	106	10	18	1	1	1	1	0	1	96	40	8	1	2	2	1	60	65	0	2	2	1
91	30	F	1	9	1	1	10	6	1	1	2	2	1	2	2	0	0	2	2	2	2	2	2	1	0	0	40	1	150	10	18	1	1	1	1	0	1	106	36	18	1	1	1	1	50	60	0	2	2	1
92	38	M	2	3	1	1	6	3	2	1	1	2	1	2	2	0	0	2	2	2	2	2	2	1	0	0	66	1	182	19	13	1	1	1	1	0	1	106	20	8	1	1	2	1	70	50	0	2	2	1
93	38	M	2	9	1	1	27	17	2	1	1	1	2	2	2	2	0	2	2	2	2	2	2	1	0	0	98	1	98	36	8	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
94	39	M	1	2	1	1	60	24	1	1	2	2	2	1	1	3	0	2	2	2	2	2	2	1	0	3	48	1	98	36	6	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
95	44	F	1	1	1	1	24	18	1	1	2	2	2	2	2	2	0	2	2	2	2	2	2	2	0	0	104	1	98	40	13	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
96	36	M	1	1	1	1	10	1	1	1	2	1	1	2	2	0	ATT	2	2	2	2	2	2	1	PT	0	60	1	286	30	255	2	2	2	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
97	40	F	1	1	1	1	36	30	1	1	2	1	1	2	1	0	0	2	2	2	2	2	2	2	0	0	48	1	98	38	8	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
98	30	M	3	4	2	1	3	0	1	1	2	2	2	2	2	0	0	2	2	2	2	2	2	2	0	0	108	1	98	35	8	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
99	34	M	1	2	1	1	3	0	1	1	1	2	2	2	2	0	0	2	2	2	2	2	2	1	0	0	98	1	86	24	0	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
100	41	F	1	1	1	1	24	14	1	1	2	2	2	2	2	0	ATT	2	2	2	2	1	2	2	PT	0	60	1	180	40	250	2	2	2	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0

KEY FOR MASTER SHEET

S.NO	VARIABLES	1	2	3	4	5	6	7	8	9
1	Education	Primary	Secondary	College						
2	Occupation	Unemployed	Labour	Farmer	Private	Govt	Professional	Student	Housewife	Driver
3	Marital	Married	Single							
4	HIV status	Positive	negative							
5	Clinical symptoms	Yes	No							
6	Other presentation	Cough	Dysphagia	FND	Blurring of vision					
7	Drugs	ATT								
8	HT/DM/CAD/CKD/TB	Yes	No							
9	Sexual promiscuous	Yes	No							
10	Substance abuse	Yes	No							
11	CXR	TB								
12	Brain imaging	Normal	CNS Lymphoma	Toxoplasmosis	TB Meningitis					
13	CSF appearance	Colourless								
14	Culture/India ink	Positive	Negative							
15	Crag/Crypto status	Positive	Negative							
16	Other CSF finding	AFB	IgG for toxoplasmosis							
17	Clinical improvement	Improved	Not improved							

INSTITUTIONAL ETHICAL COMMITTEE, STANLEY MEDICAL COLLEGE, CHENNAI-3

Title of the Work	:	Comparison of the efficacy of 3 weeks Amphotericin therapy vs 2 weeks Amphotericin therapy in HIV positive cryptococcal meningitis patients & also ascertain the impact of both on CSF parameters
Principal Investigator	:	Dr. R.Israel
Designation	:	PG in MD (GM
Department	:	General Medicine

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 28.06.2010 at the Modernised Seminar Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate form the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

SECRETARY
IEC, SMC, CHENNAI

CHAIRMAN,
IEC, SMC, CHENNAI